REMARKS

The present invention relates to, among other things, novel methods for detecting a molecule (*e.g.*, an antigen) on a cell (*e.g.*, a blood cell), and novel reagents relating thereto.

The above-captioned application is a divisional application of U.S. Patent Application No. 08/884,046 (the "parent application"), now issued as U.S. Patent No. 5,985,543, to Siegel. The instant application was filed to prosecute original claims 10-23, which are drawn to an invention not elected in the parent application. By way of Preliminary Amendment filed in this application on September 29, 1999, claims 1-9 and 24-29, were canceled.

Subsequently, in Response to Restriction Requirement mailed September 25, 2001 (Paper No. 6), Applicant elected claims 10-19 for examination in this application. Accordingly, claims 10-23 are pending in this application, claims 20-23 stand withdrawn as being drawn to non-elected inventions, and claims 10-19 are under examination.

Rejection of Claim 11 under 35 U.S.C. §112, first paragraph

Claim 11 stands rejected under 35 U.S.C. §112, first paragraph, because in the Examiner's opinion, the claim is not enabled. Further, it appears that while the rejection is only explicitly drawn only to claim 11, the other claims under examination are also rejected under §112, first paragraph, as indicated at the top of page 2 of the Office Action. Thus, for purposes of this Response, Applicant will address the rejection under 35 U.S.C. § 112, first paragraph, assuming that the rejection applies to claims 10-19. Further, the arguments provided herein with respect to claim 11 apply with equal if not greater force to claims 10 and 12-19, which relate to methods where sedimentation is by gravity (claims 10, and 12-19) instead of by centrifugation (claim 11).

In the Examiner's view, the claims are not enabled in that the specification does not support a method for detecting cell agglutination in the absence of an incubation step. Applicants respectfully submit that method as recited by claim 11, as well as those recited in claims 10 and 12-19, is enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

It is well-settled that an applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir.

1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)).

The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Applicant respectfully submits that even though a working example is not required, the specification as filed sets forth several examples where the method of claims 10-19 was extensively reduced to practice. In these examples, Applicant demonstrated that cell agglutination could be readily detected using a mixture of cells and bacteriophage expressing an antibody specific for an antigen expressed by at least a portion of the cells in the mixture. Such examples are set forth at, *inter alia*, pages 43 through 44, and Figures 4, 5, and 6. Based on this ample reduction to practice, where the law does not require <u>any</u> reduction to practice, Applicant respectfully submits that the specification as filed provides enablement for a method of detecting cell agglutination as recited in claim 11, as well as that recited in claim 10, and claims depending therefrom.

Furthermore, as pointed out previously, the law is well-settled that extensive experimentation is not undue if one of ordinary skill in the art routinely engages in such experimentation. Moreover, the high degree of skill in the art, the extensiveness of experimentation routinely performed by the artisan in that art, and the fact one skilled in the art of reference (*e.g.*, detection of cell agglutination) typically engaged in this type of experimentation at the time the application was filed, must all be considered. This is important, since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

Moreover, under the present law of enablement, generic claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), reviewing an enablement rejection of a broad claim reciting methods for producing insect proteins in cyanobacteria, the Court of Appeals for the Federal Circuit discussed enablement in the context of generic species claims:

> we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 20 USPQ2d at 1445 (emphasis added). Thus, not every species need be disclosed where one skilled in the art would be able, without undue experimentation, to determine which species possess the disclosed utility. *See also In re Druey*, 145 USPQ 219, 221 (Bd. Pat. App. & Int. 1965)("The fact that not all possible substituents encompassed by the generic language are illustrated does not preclude appellants from asserting the genus when no reasons have been advanced by the examiner to rebut appellants' assertion that all the compounds embraced by the genus will in fact have the properties ascribed to them."). Thus, each particular test condition need not be reduced to practice before the present claims are enabled.

The MPEP at § 2164.08(b), discussing inoperative subject matter, states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling.

> . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader that the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Thus, inoperative embodiments do not necessarily render a claim nonenabled as long as the experimentation required to identify the operative species is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen (HBsAg) using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known .
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically determines the assay conditions for detecting cell agglutination, one skilled in the art would not require undue experimentation to practice the invention commensurate with the scope of claims 10-19. Thus, where one skilled in the art routinely assesses and optimizes the conditions for detecting cell agglutination as disclosed in the specification as filed, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the

reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted). Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for detecting cell agglutination are disclosed and exemplified in the specification and where various conditions are extensively disclosed and reduced to practice in the specification as filed, it would not be undue experimentation to practice the method of the invention as disclosed in the present specification where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins (*i.e.*, mutated protein variants of the naturally-occurring protein) comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely determines the conditions for detecting cell agglutination, it is not undue experimentation for them to do so without the need to recite an incubation step. Similarly, where the invention discloses and, where examples demonstrate extensive reduction to practice of the invention, every single assay condition for detecting cell agglutination following the teachings provided in the specification in light of the skill in the art need not be set out before such methods can be patented. To require such onerous dissertation on matters known to the skilled artisan would not only make patent applications impracticably voluminous, but would impede progress in the useful arts as it would force applicants to write tomes of instructions that would be unnecessary to one skilled in the art to practice the invention.

Indeed, one skilled in the art of performing assays for detecting cell agglutination would routinely assess and develop the conditions for performing the assay, including, but not limited to, how much, if any, incubation was required at each step of the assay, along with other parameters such as, *e.g.*, the concentrations of reagents, temperature of the reaction, and the like. These were all routine matters for experimentation by the skilled artisan at the time the specification was filed and, thus, no undue experimentation would be required by the skilled artisan in performing such manipulations.

Additionally, Applicant respectfully points out that the reference cited by the Examiner for the proposition that it was known in the art that detecting agglutination required an incubation step, *i.e.*, U.S. Patent No. 5,491,067, to Setcavage et al., does not support that incubation is required in the novel agglutination detection methods of the invention. More specifically, the Examiner cites Setcavage et al., at column 1, lines 26-39, to support that incubation is a required step that must be recited in claims 10-19. Setcavage et al., states, in pertinent part: "For detecting antibodies in the serum or plasma of a patient, reagents containing blood cells having known antigens are mixed with a serum sample. The reactants are incubated for a period of time sufficient to permit agglutination of the red blood cells, which occurs when antibodies against those antigens are present." *Id.* at column 1, lines 26-31 (emphasis added). Applicant respectfully submits that whatever Setcavage et al., may teach about detection of unknown antibodies in a serum or plasma sample using characterized cells, these teachings are inapplicable to the present invention which relates to detection of antigens present on an uncharacterized cell using a well-characterized phage-displayed antibodies. Thus, the teachings of Setcavage et al., cannot be extended to the present invention where the reference teaches a completely different method relating to cell agglutination. That is, the present invention teaches, *inter alia*, a method for detecting cell agglutination where the phage-displayed antibody is well-characterized, and its affinity and avidity for a particular antigen present on a cell can be assessed and known in advance, such that incubation conditions, or the lack of incubation, can be readily determined by the skilled artisan. This is not possible in Setcavage et al., where the characteristics (*e.g.*, concentration, affinity, avidity, and the like) of the antibody are not known. Therefore, Setcavage et al., is not pertinent to determining enablement of the present invention where Setcavage et al., and the passage cited by the Examiner, relate to an assay (*e.g.*, detecting

unknown antibodies in serum or plasma) not at issue in the present application, which relates to using known antibodies to detect an antigen on a cell of interest.

Further, it is well-settled that recitation of an example does not in any way limit the claims to that embodiment under present patent law. Thus, the recitation in the specification at page 24, line 23, pointed out by the Examiner to support that an incubation step is required in the method of the invention, merely illustrates that in one embodiment, incubation was performed. However, it is well-settled that providing an example does not limit the invention to that example, and in no way limits the claim to that embodiment. Thus, mere recitation of an example reciting incubation does not support that claims that do not recite an incubation step are not enabled. Rather, the claims are interpreted in light of the specification as a whole and in view of the skill in the art, and are not limited to any particular exemplary embodiment provided to illustrate the invention. Otherwise, applicants for a patent would be compelled to provide numerous examples so as to avoid unwittingly narrowing their invention to any particular example set out in the specification. The present patent statute, and case law applying and expounding it, do not compel such a result.

Therefore, Applicant respectfully submits that the specification as filed amply supports that the claimed methods are enabled under 35 U.S.C. §112, first paragraph, and the rejection of claims 10-19, should be reconsidered and withdrawn.

Rejection of claim 11, pursuant to 35 U.S.C. §112, second paragraph

Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In the Examiner's opinion, claim 11 is indefinite in that it omits an essential step, *i.e.*, "incubating the mixture of cell/virus complexes with the inert particles prior to centrifugation." (Office Action at page 4). Applicant respectfully submits that claim 11 is not indefinite in any way for the following reasons.

It is settled law that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). *See also* MPEP § 2173.01. This is because "[t]he dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words, but words for things." *Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Further, applicant is entitled to

have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Therefore, applicants are entitled to define terms to describe their invention and the claims must be interpreted in light of the other parts of the application, including the disclosure in the specification and the definitions provided therein.

Applicant respectfully submits that the specification as filed makes clear that the method for detecting agglutination comprising sedimentation by centrifugation can, but need not, encompass an incubation step. That is, as previously discussed elsewhere herein, the skilled artisan, armed with the teachings provided in the specification as filed, would have understood that the reaction conditions could be readily determined for any phage-displayed antibody of interest to detect a known antigen expressed on a cell of interest present in a sample. Thus, there is absolutely nothing vague about claim 11 as presently set forth because the skilled artisan would have appreciated, at the time the specification was filed, that the method can, but need not, comprise an incubation step, and the lack of recitation of such as step does not render the claim vague in any way. Thus, recitation of an incubation step is not essential, and claim 11 would have been well understood by one skilled in the art and is not vague or indefinite in any way. Accordingly, Applicant respectfully requests that the rejection of claim 11 under 35 U.S.C. §112, second paragraph, for indefiniteness, be reconsidered and withdrawn.

Summary

Applicant respectfully submits that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 10-19, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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July 6, 2004
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